several months) and intravenous treatment (typically 3-6 weeks).

REMARKS

Any fees that may be due in connection with this application throughout its pendency may be charged to Deposit Account No. 50-1213.

The specification is amended to correct obvious typographical and spelling errors. In particular, the specification is amended to replace the terms "osmotic pressure" and "osmolarity" with the term "osmolality", at several places. The amendment finds basis in the units of measurement of solute concentration recited in the specification, "mOsm/kg", which measures "osmolality". Therefore use of the terms "osmotic pressure" or "osmolarity" to express the physical property measured by "mOsm/kg" is inappropriate. The specification is also amended to add inadvertently omitted chemical names for the tradenames of the surfactants, TWEEN® and SPAN® on page 23, paragraph 0080.

Included as an attachment is a marked-up version of the specification paragraphs, per 37 CFR §1.121. No new matter has been added.

* * *

Entry of this amendment is respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Osbakken *et al.*
Serial No.:	09/942,959
Conf. No.:	7962
Filed:	August 31, 2001
For:	*AEROSOLIZED ANTI-INFECTIVES, ANTI-INFLAMMATORIES, AND DECONGESTANTS FOR THE TREATMENT OF SINUSITIS*
Art Unit:	1616
Examiner:	DeWitty, R.

ATTACHMENT TO THE PRELIMINARY AMENDMENT
MARKED UP PARAGRAPHS (37 CFR §1.121)

IN THE SPECIFICATION:

Please amend the specification as follows:

On page 1, please amend paragraph 0002, as follows:

The present invention relates to pharmaceutical compositions comprising one or more active ingredients selected from the group consisting of anti-infective agents, anti-inflammatory agents, mucolytic agents, antihistamines, antileukotrienes, decongestants, anticholinergics and antiseptics and particularly to compositions formulated into a liquid, for example, as a solution, suspension, or emulsion, in a unit dose or in multi-dose vials for aerosol administration to treat chronic sinusitis.

On page 11-12, please amend paragraph 0037, as follows:

More than 25 antihistamine drugs are now available ("Histamine," Microsoft® Encarta® Online Encyclopedia 2000 http://encarta.msn.com® 1997-2000 Microsoft Corporation. All rights reserved.). They are categorized into the following classes:

1. Ethanolamines: diphenhydramine hydrochloride, dimenhydrinate,

carbinoxamine, clemastine fumarate, bromodiphenhydramine hydrochloride.

2. Ethylenediamines: tripelennamine hydrochloride, pyrilamine maleate, antazoline phosphate, methapyriline.
3. Alkylamines: chlorpheniramine maleate, brompheniramine maleate, dexchlorpheniramine maleate, dimethindene maleate, triprolidine hydrochloride, pheniramine maleate.
4. [Piperzines] Piperazines: cyclizine hydrochloride or lactate, meclizine hydrochloride, hydroxyzine hydrochloride, hydroxyzine pamoate, buclizine, chlorcyclizine.
5. Phenothiazines: promethazine hydrochloride, methdilazine, trimeprazine tartrate.
6. Miscellaneous: cyproheptadine, ketotifen, azatadine maleate, terfenadine, fexofenadine, astemizole.

On page 16, please amend paragraph 0053, as follows:

The present invention relates to pharmaceutical compositions that include one or more active ingredients such as an anti-infective agent, an anti-inflammatory agent, a mucolytic agent, an antihistamine, an antileukotriene, a decongestant, an anticholinergic agent, antifungal agent, and a combination of these classes of agents. Anti-infective agents contemplated by the present invention include, but are not limited to antibiotics, anti-virals, non-antibiotic antimicrobials, and [antiseptics Anti-inflammatory] antiseptics. Anti-inflammatory agents contemplated by the present invention include but are not limited to steroidal and nonsteroidal anti-inflammatory agents, and mast cell stabilizers. Antifungal agents contemplated by the present invention include but are not limited to amphotericin and azole antifungals, such as itraconazole, miconazole, and fluconazole. Combinations of antibiotics are also contemplated by the present invention.

On page 17, please amend paragraph 0057, as follows:

Generally, it is contemplated that formulations according to the present invention will preferably have a pH in the range of about 3.0 to 8.5; an [osmotic pressure] osmolality of the solution or suspension between about 150 mOsm/kg to 880 mOsm/kg; and [a] an NaCl equivalency to the solution or suspension is preferably between about 0.2% NaCl to 3.0% NaCl.

On page 19, please amend paragraph 0067, as follows:

A surprising discovery made by the inventors was that the surface tension of the solution or suspension prepared for inhalation needed to be adjusted to achieve optimal results. To achieve effective deposition of medication within the sinuses it is preferable to have the surface tension of the solution or suspension for aerosolization [be] adjusted with surfactants to less than about 70 dynes/cm, more preferably less than about 55 dynes/cm, even more preferably less than about 50 dynes/cm and most preferably [between] less than about 45 dynes/cm. Even lower surface tensions are contemplated. In one embodiment, the preferred surface tension is between about 10 to 40 dynes/cm. In another embodiment, the preferred surface tension is between about 20 to 40 dynes/cm. Most preferably, the surface tension is between about 30 to 40 dynes/cm.

On page 20, please amend paragraph 0069, as follows:

These compositions ideally will be formulated into a liquid (solution, suspension, emulsion *etc.*) in a unit dose or multi-dose vial for aerosol administration to the nasal cavity and sinuses and [being] will be packaged with directions for its use in the treatment of sinusitis. The compositions include powder that can be mixed with a diluent to produce a liquid. Appropriate compositions for this purpose will be formulated by using surfactants, NaCl, or other chemical entities to adjust the liquid for administration to have the following properties:

- surface tension preferably less than about 70 dynes/cm, more preferably

less than about 55 dynes/cm, even more preferably less than about 50 dynes/cm, most preferably less than about 45 dynes/cm. Even lower surface tensions are contemplated by the present invention. In one embodiment, the preferred surface tension is between about 10 to 40 dynes/cm. In another embodiment, the preferred surface tension is between about 20 to 40 dynes/cm. Most preferably, the surface tension is between about 30 to 40 dynes/cm.

- [osmotic pressure] osmolality between about 200 mOsm/kg to 880 mOsm/kg, more preferably between about 300 mOsm/kg to 700 mOsm/kg and most preferably between about 400 mOsm/kg to 550 mOsm/kg.
- NaCl equivalency of the solution or suspension preferably between about 0.2% NaCl and 3.0% NaCl, more preferably between about 0.45% NaCl and 1.8% NaCl and most preferably between about 0.9% NaCl and 1.7% NaCl.
- pH preferably between about 3.0 and 8.5, but may vary according to the properties of the medication used.

On pages 21-22, please amend paragraphs 0072-0075, as follows:

B. [Osmotic Pressure] Osmolality:

Optimal [osmotic pressure] osmolality helps to reduce damage to the epithelia cilia and mucosa of the sinuses. Although often not present in chronic sinusitis patients, epithelia cilia perform a useful function in the sinuses by moving mucosal fluid out of the sinuses.

For purposes of preparing formulations according to the present invention, [osmotic pressure] osmolality may be measured by using an Osmometer. If necessary, [osmotic pressure] osmolality may then be raised to fall within a preferred range by adding NaCl dextrose, or other salts to the liquid.

C. Sodium Chloride Equivalency:

Optimal NaCl equivalency (tonicity) works to reduce swelling in the sinuses and nasal cavity by drawing water from the nasal and sinus epithelia, reducing swelling. NaCl equivalency below 0.9% (hypotonic) may cause swelling in the epithelia of the nasal cavity and sinuses. NaCl equivalency above 3.0% would raise the tonicity and [osmotic pressure] osmolality above desirable levels and may cause a burning sensation.

For purposes of preparing formulations according to the present invention, NaCl equivalency will closely follow [osmotic pressure] osmolality and can be measured using the methods described in section B above.

On page 23, please amend paragraph 0078, as follows:

After determining the medications to be used in the formulation, each ingredient is weighed/measured out individually, added together, mixed with diluent, for example, sterile water, and filtered with a coarse filter and then a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron). The preparation is then tested to ensure that it is within the parameters established for surface tension, [osmolarity] osmolality, pH, and sodium chloride equivalency. This is done by using the appropriate equipment for each test as noted in Sections A to D above. To prepare a unit dose, the ingredients of such formulations generally will be dissolved in a solvent such as water or saline solution, in a volume between about 0.5 and 6.0 mls, more preferably between about 2 and 4 mls and most preferably between about 2.5 and 3.5 mls.

On page 23, please amend paragraphs 0080-0081, as follows:

Surfactants can be used as dispersing agents, solubilizing agents, and spreading agents. Some examples of surfactants are: PEG (polyethylene glycol) 400 [,] ; Sodium lauryl sulfate [, span (20-40-60 etc.),]; sorbitan laurate, sorbitan palmitate, sorbitan stearate available under the tradename Spans®(20-40-60 etc.); [tweens (polysorbates, 20-40-60 etc),] polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate,

polyoxyethylene (20) sorbitan monostearate available under the tradename Tweens® (polysorbates, 20-40-60 etc.); tyloxapol [,] ; propylene glycol [,] ; and Benzalkonium chloride. Contemplated surfactants include any compound or agent that lowers the surface tension of a composition.

The purpose of using surfactants in the preferred formulations of the present invention is to adjust the surface tension of the aerosolized particles so that the maximum amount of medication is deposited within the sinus cavities. If the surface tension is reduced too much, the majority of the particles will deposit in the nasal cavity, conversely if the surface tension is too [high the] high, the particles go directly to the lungs without depositing in the nasal sinuses.

On page 24, please amend paragraphs 0083-0084 as follows:

Surfactants can act as [a] solubilizing [agent] agents by forming micelles. For example, a surfactant with a high HLB would be used to increase the solubility of an oil in an aqueous medium. The lipophilic portion of the surfactant would entrap the oil in the lipophilic (interior) portion of the micelle. The hydrophilic portion of the surfactant surrounding the oil globule would, in turn, be exposed to the aqueous phase.

An HLB value of 10 or higher means that the agent is primarily hydrophilic, while an HLB value of less than 10 means it would be lipophilic. For example, [spans] Spans® have HLB values ranging from 1.8 to 8.6, which is indicative of oil soluble [for] or oil dispersible molecules. Consequently, the oil phase will predominate and a water/oil emulsion will be formed. [Tweens] Tweens® have HLB values that range from 9.6 to 16.7, which is characteristic of water-soluble or water dispersible molecules. Therefore, the water phase will predominate and oil/water emulsions will be formed.

On page 27, please amend paragraph 0104, as follows:

Providing potassium iodide according to the present invention is believed to be a more effective way to provide the medication to a greater area within

the sinus cavity resulting in relief of bacteria, fungi, viruses, spores, protozoa and [yeasts] yeast infections.

On page 30, please amend paragraph 0121, as follows:

Anticholinergics prevent the increases in intracellular concentrations of cyclic guanosine monophosphate, which are caused by interaction of acetylcholine with the muscarinic receptor of some smooth muscles. Specifically ipratropium has been shown to be [affective] effective in patients with allergic or nonallergic perennial rhinitis, where studies showed there was a statistically significant decrease in the severity and duration of rhinorrhea.

On page 32, please amend paragraph 0133, as follows:

Preferably the formulation will also be evaluated using E tables from sources known to practitioners skilled in the pharmaceutical arts, such as *Remington: The Science and Practice of Pharmacy* or other suitable pharmaceutical text to calculate its sodium chloride equivalence to ensure that it is in the preferred range of 0.2% to 1.5%. Similarly, the [osmolarity] osmolality is checked to ensure that it falls within the preferred range of about 300 to 880 mOsm/kg. If [osmolarity] osmolality falls outside of this range, the polysorbate 20 component may be decreased until the preferred conditions are met.

On page 33, please amend paragraph 0136, as follows:

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On page 33, please amend paragraph 0139, as follows:

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On page 34, please amend paragraph 0142, as follows:

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity]

osmolality within preferred ranges or to preferred levels.

On page 34, please amend paragraph 0145, as follows:

As a sixth example, cefoperazone and oxymetazoline are formulated in 3 ml of sterile water for injection to provide an antibiotic formulated with a decongestant. This formulation is prepared under a laminar flow hood by following these steps: 1) weigh out sufficient powder of cefoperazone to make 28 doses of 600 mg each (16.8 g) allowing 5% overage for compounding loss; 2) weigh out sufficient powder of [oxymetazonline] oxymetazoline to make 28 doses of 0.5 mg each (14 mg) allowing 5% overage for compounding loss; 3) combine the powders together; 4) QS ad with sterile water to 84 ml allowing 5% overage for compounding loss; 5) add benzalkonium chloride 0.02% (0.02 gm/100 ml of liquid). The final compounded liquid mixture is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

On page 35, please amend paragraph 0146, as follows:

The formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On page 35, please amend paragraph 0149, as follows:

The surface tension of the formulation is measured using a ring tensiometer. The preferable range is 10 to 70 dynes/cm. The formulation may be adjusted with a surfactant, for example, polysorbate 20. Using a pH meter, the formulation is tested for the desirable pH, preferably in the range of about 3.0 to 8.5. The pH is adjusted with appropriate acids, bases and appropriate buffers as needed according to conventional compounding practices. In addition the formulation will also be evaluated using E tables from sources known to practitioners skilled in the pharmaceutical arts, such as *Remington: Science and Practice of Pharmacy* or other suitable pharmaceutical text to calculate its sodium chloride equivalence to ensure that it is in the preferred range of 0.9% to 3.0%. Similarly, the [Osmolarity] osmolality is checked to ensure that it falls

within the preferred range of about 300 to 880 mOsm/kg. If [osmolarity] osmolality falls outside of this range, the polysorbate 20 component may be decreased until the preferred conditions are met.

On page 36, please amend paragraph 0152, as follows:

The surface tension of the formulation is measured using a ring tensiometer. The preferable range is 10 to 70 dynes/cm. The formulation may be adjusted with a surfactant if necessary using, for example, polysorbate 20. Using a pH meter, the formulation is tested for the desirable pH, preferably in the range of about 3.0 to 8.5. The pH is adjusted with appropriate acids, bases and appropriate buffers as needed according to conventional compounding practices. In addition the formulation will also be evaluated using E tables from sources known to practitioners skilled in the pharmaceutical arts, such as *Remington.- Science and Practice of Pharmacy* or other suitable pharmaceutical text to calculate its sodium chloride equivalence to ensure that it is in the preferred range of 0.9% to 3.0%. Similarly, the [osmolarity] osmolality is checked to ensure that it falls within the preferred range of about 300 to 880 mOsm/kg. If [osmolarity] osmolality falls outside of this range, the polysorbate 20 component may be decreased until the preferred conditions are met.

On page 36, please amend paragraph 0154, as follows:

This formulation may be compounded under a laminar flow hood by performing the following steps: 1) weigh out a sufficient quantity of gentamicin powder to prepare 42 doses (3990 mg) with 5% overage to account for loss during compounding; 2) weigh out a sufficient quantity of cefuroxime powder to prepare 42 doses (11,970 mg) with 5% overage to account for loss during compounding; 3) mix the powders and QS ad to 252 ml with sterile water for injection; 4) test physical properties as above and adjust as necessary; and 5) sterile filter with 0.22 micron filter.

On page 37, please amend paragraph 0158, as follows:

This formulation is prepared under a laminar flow hood by following these

steps: 1) weigh out sufficient powder of ipratropium bromide to provide the number of doses needed at 0.075 mg per dose with 5% overage for compounding losses; 2) using one half of the total volume of liquid to be made, dissolve ipratropium bromide in normal saline (use 5% overage for compounding losses); 3) weigh out sufficient powder of betamethasone phosphate to provide the number of doses needed at 0.4 mg per dose betamethasone activity also allowing for 5% overage for compounding losses; the activity is noted on the manufacturer container label or can be gotten from the supplier; 4) using one half of the total volume of liquid to be made, dissolve betamethasone in sterile water with 5% overage for compounding losses; and 5) combine the two solutions or suspensions. The final compounded liquid mixture is filtered using a 0.22 micron filter before dispensing in 3 ml aliquots to the unit of use (unit dose) containers. This formulation is tested as described above and adjustments made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On pages 37-38, please amend paragraph 0160, as follows:

This formulation is prepared under a laminar flow hood by following these steps: 1) weigh out sufficient powder of taurolidine to provide 80 mg per dose with 5% overage for compounding losses; 2) dissolve the powder using a suitable diluent (sterile water, normal saline, povidone) allowing 5% overage for compounding; and 3) divide the resultant solution into 3ml aliquots to the unit of use containers. The formulation is tested as described earlier. Adjustments are made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On page 38, please amend paragraph 0164, as follows:

The formulation is compounded under a laminar flow hood [be] by performing the following steps: 1) weigh out sufficient quantity of cromolyn powder to make the number of doses required, adding 5% for compounding losses; 2) weigh out sufficient powder of acetylcysteine to make the number of

doses required, adding 5% for compounding losses; and 3) combine the powders and QS ad with sterile water to sufficient volume to make the number of 3 ml doses asked for in the prescription. The final solution is filtered using a 0.22 micron filter before placing in a unit of use (unit dose) container.

On page 38, please amend paragraph 0165, as follows:

The formulation is tested as described above. Adjustments are made to bring surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality within preferred ranges or to preferred levels.

On page 40, please replace paragraph 0176, as follows:

The preferred treatment is the antibiotic (adjusted for the proper surface tension, pH, sodium chloride equivalence, and [osmolarity] osmolality) that most effectively kills the bacteria or fungus as determined by culture and sensitivity, administered once to three times per day for a duration of 5 to 10 minutes per each treatment (See Table 1).

On page 40, please amend paragraph 0178, as follows:

The typical otolaryngologist when treating chronic sinusitis prescribes antibiotics until the patient is symptom free by physical exam plus an additional seven days. The problem that occurs with respect to sinus infections is that, if the infection is not completely resolved, the patient will have a recurrence the next time his/her immune system is challenged, *i.e.*, the next upper respiratory infection that results in obstruction of the osteomeatal complex, impairs [mucociliory] mucociliary clearance and causes over production of secretions. Thus, the preferred method of determining resolution of the infection is to reculture the sinuses endoscopically and have the laboratory report come back negative, *i.e.*, reporting no growth of pathogenic microorganisms. The present inventors have discovered that aerosolization should lead to less resistance exhibited by bacteria due to the fewer times they are exposed to the antibiotic, and such exposure occurs at lower dosages and for shorter periods of time of aerosolized administration (typically 1-3 weeks) as compared to oral (typically 3

weeks to several months) and intravenous treatment (typically 3-6 weeks).